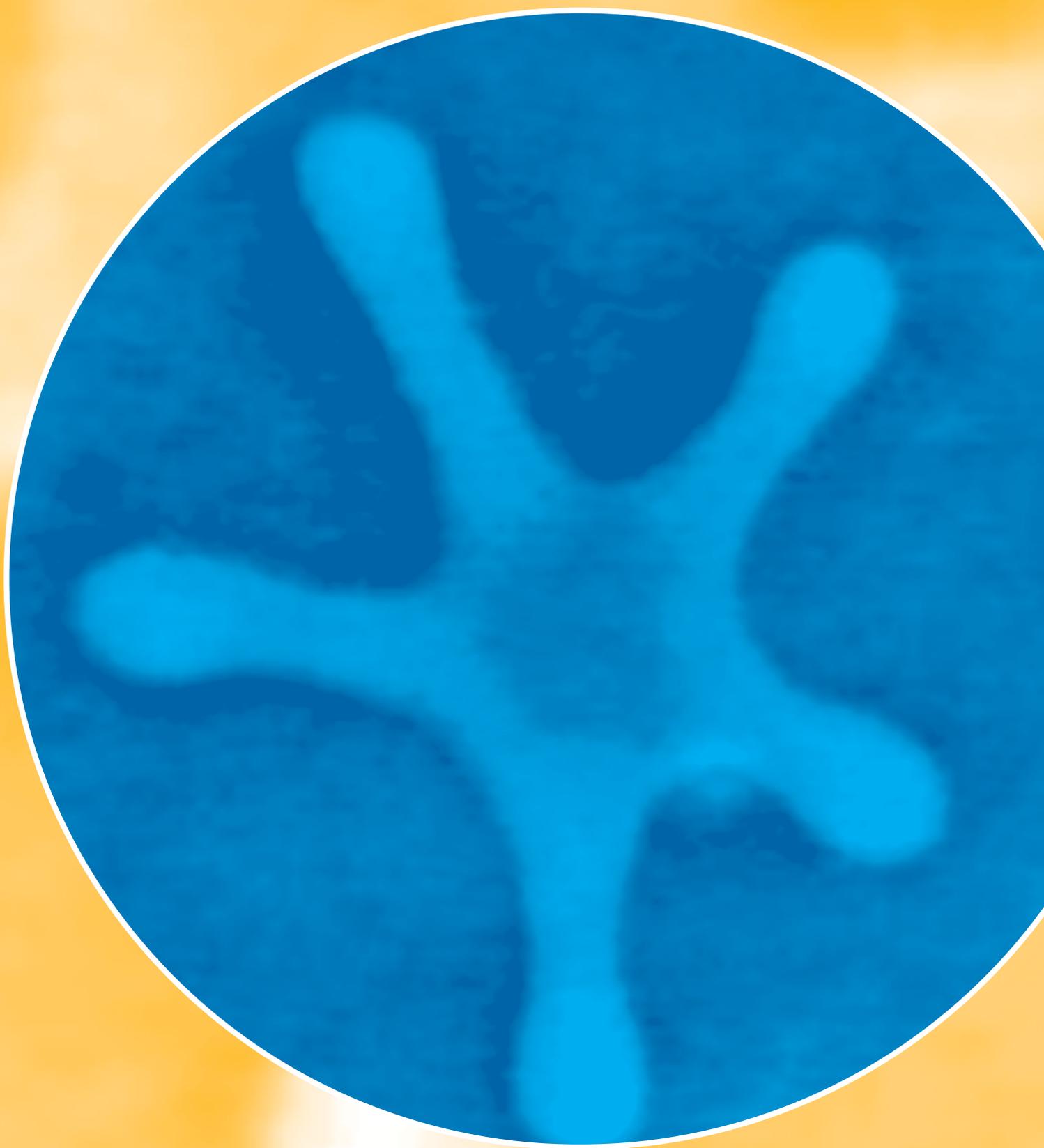


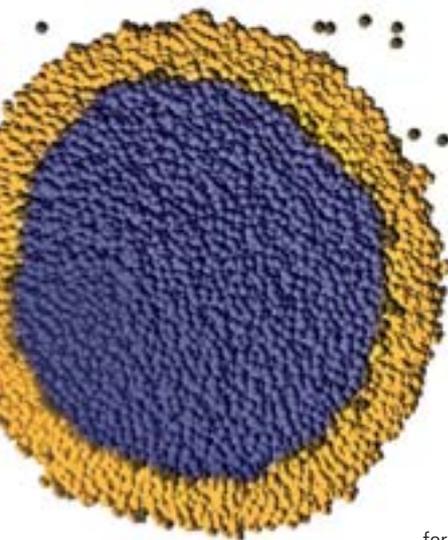


# THEORY

THEORY



# Research in the Theory Department



Research in the theory department is focused on generic aspects of colloids and interfaces such as structure formation, polymorphism, morphological transitions, entropic forces, and active behavior. In many cases, our theoretical models are inspired by the colloidal architecture of biomatter, which corresponds to the basic levels of life and which includes assemblies and super-assemblies of biomolecules as previously described on page 13.

The conceptual framework for the understanding of these systems and their cooperative behavior is provided by statistical physics which includes thermodynamics, statistical mechanics, and stochastic processes.

Most associates of the theory department perform theoretical work using the analytical and numerical methods of theoretical physics. In addition, some experimental work is carried out in our membrane lab, using optical microscopy, micropipettes, and isothermal titration calorimetry, and in the DESY lab of the MPI.

The theory department is divided into several groups. During 2001 and 2002, seven groups were primarily funded by the Max Planck Society:

- Christian Seidel (theory, polymers and polyelectrolytes)
- Roland Netz, now at the University of Munich (theory, polyelectrolytes and charged systems)
- Jan Kierfeld (theory, polymers and filaments)
- Rumiana Dimova (experiment, membranes and vesicles)
- Julian Shillcock (theory, supramolecular modeling)
- Angelo Valleriani (theory, evolution), now program coordinator of the IMPRS on „Biomimetic Systems“
- Thomas Gruhn (theory, membranes and vesicles)
- Thomas Weikl (theory, proteins and membranes)

In addition, three groups were primarily funded externally:

- Hans-Günther Döbereiner, now at Columbia University (experiment, membranes and vesicles), funded by Heisenberg fellowship of DFG
- Willi Fenzl at DESY lab (experiment, X-ray scattering), funded by BMBF
- Ulrich Schwarz (theory, membranes and cells), funded by Emmy Noether fellowship of DFG

## Structural Hierarchy and Theoretical Concepts

The structural hierarchy of colloids and interfaces implies a hierarchy of theoretical concepts. Indeed, for each level of this hierarchy, one needs to develop a separate description which identifies the useful concepts and the relevant parameters for that level. This is a challenge which is not always appreciated.

In fact, one often hears statements of the sort that, in principle, any system consisting of many atoms is governed by a 'huge' Schrödinger equation which describes the quantum-mechanical motion of the atomic nuclei and of the electrons. However, even if we were able to obtain a complete solution for the quantum-mechanical motion of all the nuclei and electrons, we would not be able to understand the meaning of this solution. Indeed, such a complete solution would represent an enormous amount of mostly useless information. Therefore, even if we had no technical problems with such a solution, we would still have to identify the various structural levels and the concepts and parameters which are appropriate for those levels.

## Top-Down: Thermodynamics of Interfaces and Membranes

Thermodynamics represents a very robust theoretical framework which provides a top-down route into the colloidal regime and which depends on a relatively small number of parameters. Using this framework in the micrometer regime, interfaces can be characterized by their Laplace pressure, interfacial tension, and contact angles. This framework is also appropriate to describe wetting morphologies on structured surfaces as we have shown during the last couple of years.

There are two simple extensions of this framework: (i) In the nanometer regime, the wetting morphologies are also affected by the line tension of the contact line which one must include as an additional parameter in the thermodynamic description; and (ii) Fluid membranes such as lipid bilayers can be understood using the same theoretical framework if one includes the bending energies with depend on membrane curvature. In the simplest case, this involves only one additional parameter, the bending rigidity of the membrane.

### **Bottom-Up: Statistical Mechanics of Supramolecular Structures**

The bottom-up approach starts from coarse-grained models for molecules or monomers. Linear chains of such monomers provide relatively simple models for homo- and copolymers. Membranes can be modeled on the nanometer scale using simplified amphiphilic molecules which assemble into bilayers. On larger scales, they behave as flexible elastic sheets which can be characterized by their bending rigidity. In both cases, one can include several components in order to mimic the behavior of multicomponent biomembranes.

These models are studied using a wide range of theoretical methods: variational methods to determine the most probable state; scaling arguments and self-consistent theories; transfer matrix methods for 1-dimensional polymers and filaments; field-theoretic methods; computer simulations based on Monte Carlo, Molecular Dynamics, and Dissipative Particle Dynamics.

Using the latter method it is now possible to simulate vesicles with a diameter of about 30 nanometers.

### **Brownian Motion and Entropic Forces**

At finite temperatures, all colloidal particles undergo Brownian motion as a result of thermally-excited collisions with the solvent molecules. Likewise, flexible colloids such as membranes and filaments undergo thermally-excited shape fluctuations which represent the Brownian motion of many coupled degrees of freedom. These shape fluctuations lead to entropically induced forces which compete with the attractive van der Waals or electrostatic forces between different colloidal structures.

The competition between molecular interactions and entropic forces has been recently studied for the adhesion of vesicles, for the sticker-mediated adhesion of membranes, and for the adsorption and bundling of semiflexible polymers or filaments.

In all cases, one finds that the entropic contributions renormalize the molecular interactions and lead to structural transitions within these systems.

In the case of membrane adhesion mediated by stickers and repellers, sticker-rich domains appear in the contact area and form certain patterns with a characteristic time evolution. A similar pattern formation process has been recently observed for the immunological synapse between cells of the immune system.

### **Active Behavior of Colloids**

Biological cells are very active: They can easily deform their shape, move, crawl, and grab onto underlying surfaces. Likewise, the intercellular arrangement of vesicles and organelles is constantly reshuffled and one observes heavy traffic of these colloidal objects. One extreme case is cell division (mitosis) which leads to the spectacular segregation of chromosomes. All of these processes are based on the cooperative behavior of active nanostructures such as filament monomers and molecular motors.

We have recently studied several aspects of this active behavior theoretically: ratchet models for the force generation by motors; lattice models for the transport by molecular motors in open and closed compartment; motor traffic involving the collective transport of many cargo particles; the formation of traffic jams arising from the strong adsorption of the motors onto the filaments; active phase transitions induced by changes in the boundary conditions as the motors enter and leave the compartments; active pattern formation in closed compartments.

Current projects on active biomimetic systems include: active force generation by polymerization; active noise of filaments and membranes; active assembly and disassembly of filaments and motors.

For more information, see the following, more detailed reports of some of our projects and the web sites:

<http://www.mpikg-golm.mpg.de/th/>

<http://www.mpikg-golm.mpg.de/lipowsky>

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# Wetting Phenomena at Structured Surfaces



Many experimental methods have been developed by which one can prepare chemically structured substrates with patterns of lyophilic (or liquid attracting) and lyophobic (or liquid repelling) surface domains. The linear size of the surface domains can be varied over a wide range of length scales from the millimeter down to the nanometer regime. We have recently discovered that such chemically structured surfaces lead to morphological wetting transitions at which the wetting layer changes its shape or morphology in a characteristic and typically abrupt manner [1, 2].

From the theoretical point of view, these wetting morphologies correspond to bifurcations of mean curvature surfaces which are pinned along their edges by the surface domain boundaries.

Presumably the simplest surface domain pattern consists of a single lyophilic stripe on a lyophobic surface. The stripe has width  $L_1$  and has a length which is large compared to  $L_1$ . The lyophilic stripe and the lyophobic substrate are characterized by different contact angles  $\theta_\gamma$  and  $\theta_\delta$  respectively. Now, imagine that we start to deposit liquid  $\beta$  on the lyophilic stripe.

## 'Painting' Striped Surface Domains

The liquid will first form a small droplet which grows until its contact line touches the boundary of the surface domain. What happens as one continues to add liquid and the droplet continues to grow?

It turns out that the subsequent evolution of the wetting layer morphology depends in a very sensitive way on the contact angle  $\theta_\gamma$  of the lyophilic stripe. [3] Indeed, this contact angle exhibits a threshold value  $\theta_{ch}(\infty)$  which separates two different wetting regimes. These two regimes are characterized by qualitatively different behavior as the volume of the deposited liquid is further increased. If the stripe has contact angle  $\theta_\gamma < \theta_{ch}(\infty)$ , the wetting layer forms a channel which becomes longer and longer as one deposits more and more liquid. For  $\theta_\gamma > \theta_{ch}(\infty)$ , on the other hand, such a long channel cannot be attained but only a short one which gradually transforms into a localized droplet. In other words, it is easy to 'paint' long  $\gamma$  stripes provided  $\theta_\gamma < \theta_{ch}(\infty)$  but it is impossible to do so for  $\theta_\gamma > \theta_{ch}(\infty)$ . The corresponding bifurcation diagram is shown in Fig. 1.

## Liquid Bridges in Structured Pores

Another geometry which can be realized experimentally are slit pores and slabs bounded by structured surfaces. The simplest pattern of surface domains consists of a single pair of opposing lyophilic stripes.

If the striped surface domains are relatively long, one may often ignore effects arising from their ends. In such a situation, the wetting morphologies are translationally invariant parallel to the stripes and are completely determined by their cross-section. However, if one takes the finite length of the surface stripes into account, one often finds bridges which are localized in space and, thus, are far from any translationally invariant state; one example is shown in Fig. 2. [4]

## Line Tension Effects

As one studies smaller and smaller systems, the wetting morphologies will also be affected by the line tension, i.e., by the free energy of the contact line. The contact angle along this line satisfies a generalized Young equation which we have derived for the most general case of topologically rough and/or chemically patterned substrates. [5]

Our equation for the contact angle contains a new term which has been recently confirmed experimentally by the group of Stefan Herminghaus, see Langmuir 18, 9771 (2002).

## Nucleation and Growth

Wetting is intimately related to surface nucleation. Thus, the nucleation at chemically structured surfaces exhibits new and interesting features which reflect the different droplet patterns which can be formed on these surfaces. One particularly interesting aspect is that these nucleation processes can lead to metastable wetting morphologies.

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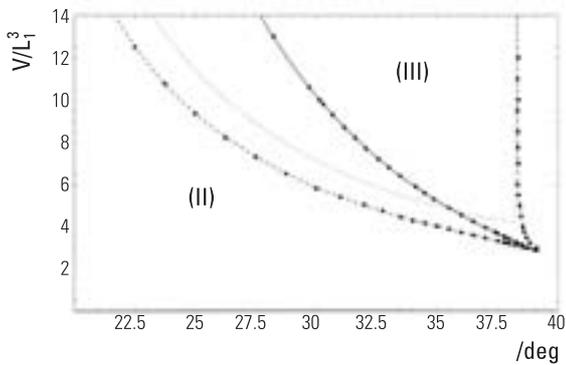


Fig. 1: Bifurcation diagram for liquid morphologies on one lyophilic stripe. The two parameters  $\theta_\gamma$  and  $V/L^3$  are the contact angle on the lyophilic stripe and the reduced volume of the liquid phase, respectively. The full line represents the line of discontinuous transitions from channel states (II) to bulge states (III). The dashed lines represent the instability lines for these two morphologies. The dotted lines are analytical estimates.

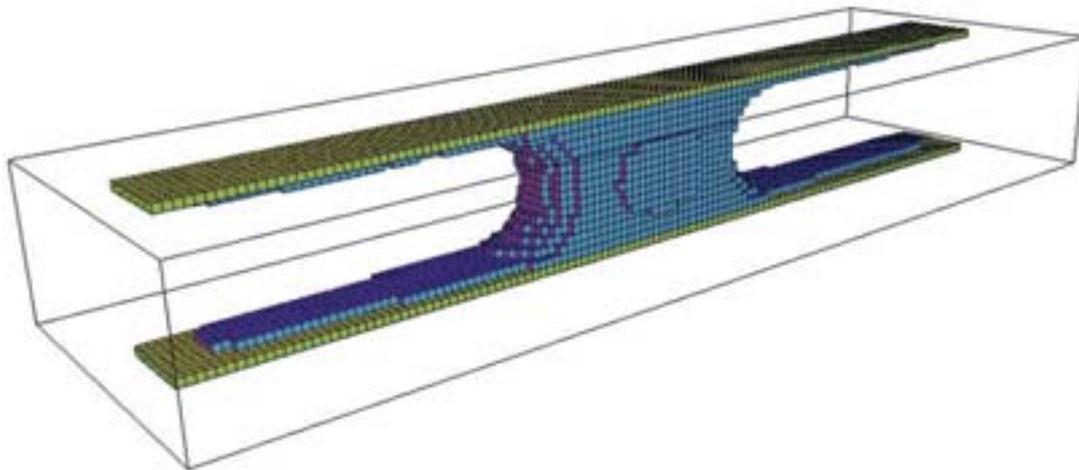


Fig. 2: Localized bridge within a slit pore or slab bounded by two structured surfaces with a lyophilic  $\gamma$  stripe as obtained from lattice gas simulations.

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# Wetting Transitions of Hydrocarbons on Water



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The wetting behavior of hydrocarbons on water is exceptional both from an experimental and theoretical point of view. Wetting transitions of pentane, hexane and heptane on water have been studied by the group of D. Bonn using ellipsometry as an experimental technique [1-3]. After a discontinuous jump from a microscopically thin film to a film with about 10 nm thickness, a continuous increase of the film thickness with increasing temperature up to 100 nm for pentane and 30 nm for hexane has been observed. The authors of Ref. [1-3] conclude that this continuous increase is indicative for a continuous wetting transition. This conclusion is mainly based on a calculation in which the nonretarded van der Waals interaction is superposed with a next-to-leading term  $b(T)d^3$ . Although this procedure has been used in a lot of theoretical papers, it is not recommended, because especially for hydrocarbons on water, the film thickness is determined by the interplay of the nonretarded static and the retarded dispersion interaction, which can even have a different sign.

Recently the dielectric function of water has been experimentally measured over a large energy range using inelastic x-ray scattering experiments [4, 5]. Using these data the dispersion part of the van der Waals interaction of a pentane film on water from the triple point up to the critical point of pentane has been calculated.

In Fig. 1 the result for a temperature slightly below the wetting transition is shown together with the static part of the van der Waals interaction. For a small film thickness the dispersion part is already positive below the wetting transition. For an intermediate film thickness above about 5 nm, the dispersion part becomes negative. Extrapolating the nonretarded dispersion interaction to film thicknesses beyond about 1 nm is therefore not meaningful. For a large film thickness beyond 100 nm the repulsive static van der Waals interaction dominates. The results of our calculation show that a wetting transition of hydrocarbons on water cannot be continuous because both the dispersion and the static part are repulsive at large film thickness already below the wetting transition. The wetting transitions of alkanes on water belong to a scenario, where the film thickness increases up to large values but finally jumps discontinuously to infinity. It is also observed that the temperature of the wetting transition is higher than the temperature, where the nonretarded van der Waals interaction changes its sign.

If the wetting transition of hydrocarbons on water would be in fact continuous, one has to look for a mechanism to cancel the static van der Waals interaction. Electrolytes dissolved in the liquid film could screen the static van der Waals interaction, but their solubility is very low in alkanes. But even if a fluctuation induced attraction like the acoustical casimir effect would balance the static interaction, the dispersion part alone is repulsive at large film thickness due to the very different dielectric susceptibilities of water and alkanes for infrared frequencies.

The temperature dependence of the measured film thickness of pentane and hexane on water does not agree well with a power law with an exponent of -1 as expected from a superposition of the nonretarded van der Waals interaction with a term  $b(T)d^3$ . For the case of hexane on water containing 1.5 M NaCl this has been already mentioned in [2], but there is no reason why pentane should show an exponent -1 and hexane not. For pentane on water the Log-Log plot presented in Fig. 1 of [1] is not convincing. Moreover, if one combines data, which are presented in [2] with those of [1], the deviation from a power law becomes better visible. It is now clearly seen that the film thickness of pentane and hexane on water is increasing very slowly over a temperature range of about 10-20 K after a discontinuous pretransition. Then, a steep increase of the film thickness occurs. DLP theory predicts film thicknesses which are not far from the observed ones, but they fail to predict the observed temperature dependence. This indicates that a quantitative prediction of the temperature dependent film thickness of alkanes on water has to go beyond the sharp kink approximation. In turn this would also affect the evaluation of the ellipsometric data.

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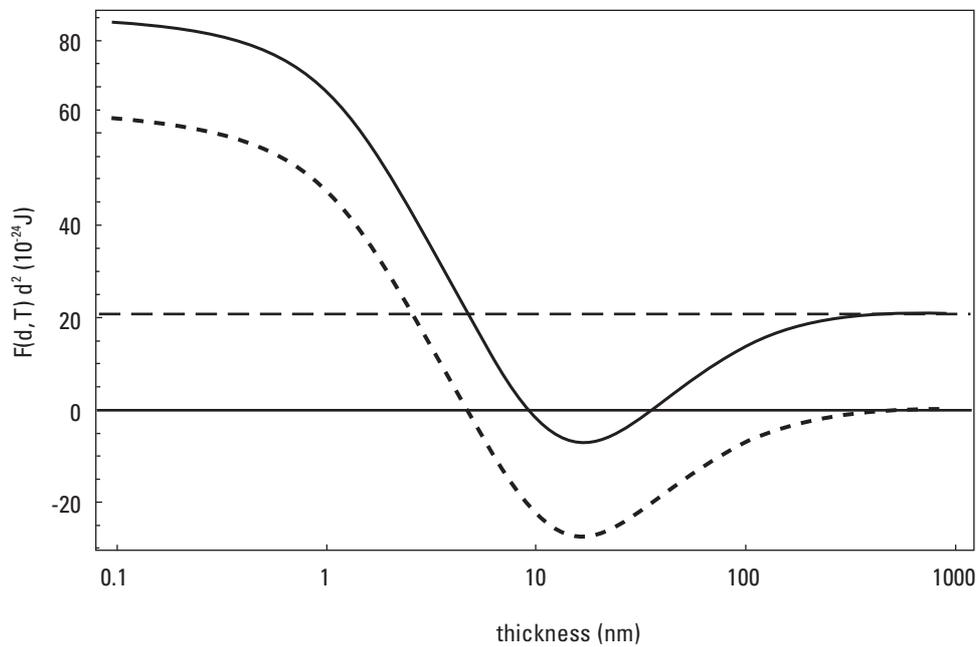


Fig. 1: Van der Waals interaction of a pentane film on water close to the wetting transition, multiplied with the square of the film thickness. The dashed line represents the static part, the dotted line the dispersion part and the full line the sum of both parts.

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# Mesosopic Simulations of Biomimetic Membranes



Lipid bilayer membranes surround living cells, protecting their interior from the outside world. They are much more than a static structural component, however, in that their composition and dynamics influence membrane-bound proteins, and contribute to the remarkable material properties of cells such as red blood cells. Bilayer membranes also surround artificial vesicles, and have been constructed out of

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non-biological amphiphiles (zu Putlitz et al., 2000), and diblock copolymers (Discher et al., 2000). These membranes continually undulate owing to the thermal motion of their constituent lipids. Thermal forces combine with specific molecular forces to create complex, dynamic, multi-component systems. Dynamic processes taking place within a membrane can involve cooperative changes over distances large compared to the molecular size, and occur on time-scales much longer than molecular vibrational periods.

Biomimetic membranes surround vesicles and artificial cells, and have many properties in common with natural membranes. Because they usually contain only one or a few types of molecule, they are much simpler to investigate experimentally, and so are used as model systems. As a result of their experimental importance, there is a great demand for a theoretical understanding of the dependence of membrane properties on their composition and the architecture of their constituent molecules. The rapid increases in the speed and memory capacity of computing technology in the last decade has permitted the development of new techniques for investigating the material properties of biomimetic membranes, of which we are using two: Coarse-grained Molecular Dynamics (MD) and Dissipative Particle Dynamics (DPD) simulations.

Traditional MD simulations are limited to a few thousand atoms even with the fastest current computers. This limitation arises from the hard-core interaction at the heart of the interatomic potentials used to represent the interactions between molecules. This necessitates a small time-step, to avoid huge forces developing when two atoms approach closely, which limits both the spatial and temporal extent of the simulation. Coarse-grained Molecular Dynamics keeps the potentials of the classical MD but treats the particles in the simulation as groups of atoms instead of individual atoms. This leads to an increase in the spatial size of system that can be simulated.

Using this technique, we have measured the shape fluctuations of a patch of lipid bilayer containing 1152 lipid molecules. The membranes exhibit long wavelength fluctuations that significantly affect their bending stiffness. Time-dependent phenomena, such as the lipid diffusion coefficient, of two-component membranes have also been studied and recently submitted for publication (Imparato, Shillcock and Lipowsky, 2002). However, these simulations are still limited in space and time by the potentials.

Moving further into the mesoscopic realm, DPD simulations are based on the premise that at length scales much larger than the atomic, which encompasses many cellular

processes of interest, such as cell adhesion, rupture and fusion, the motion of individual atoms is irrelevant. Averaging over these small-scale motions loses detailed information but greatly increases the length and time scales accessible to the simulations. We have used DPD to investigate the material properties of lipid bilayer patches and complete vesicles, comparing the results with traditional Molecular Dynamics simulations where possible. The elastic properties of a bilayer patch containing over 3000 lipids agree well with coarse-grained MD as a recent publication of our group shows (Shillcock and Lipowsky, 2002). Having thus validated the technique, we are now investigating the process of membrane fusion.

Fusion of lipid bilayers is a fundamental process in many kinds of cell, ranging from synaptic vesicle fusion in neurons to viral penetration of host cells. Fusion events typically involve proteins, although the molecular details of their action remains unclear.

Fusion of artificial vesicles has been promoted, in the absence of proteins, by several means, such as distributing divalent anions between the two fusing vesicles; employing exotic triple-chained amphiphiles in the fusing vesicles; and inducing a Marangoni flow of lipids away from the fusion zone as a consequence of the dehydrating effects of non-adsorbing polymers close to the fusing bilayers (Safran et al., 2001). Cells and vesicles do not routinely fuse with one another, showing that the lamella phase of lipid bilayers is normally stable against such processes; and yet the lamella phase can be driven along a pathway that, locally, promotes mixing of the bilayers and the formation of a pore connecting the interior volumes. The detailed structural rearrangements of lipid molecules that occur on the path to fusion are still a mystery. We are using DPD simulations to study the fusion of a vesicle to a planar bilayer induced by condensing a patch of lipids far from the fusion zone in a simutational analog of the Marangoni effect mentioned above.

When a relaxed vesicle containing approximately 6400 lipids is placed near a tense lipid bilayer, which contains 3600 lipids, its shape fluctuations cause it to encounter the proximal bilayer leaflet.

Once a few lipids bridge the water gap between the two membranes, we externally induce a surface tension gradient in the planar membrane's proximal leaflet resulting in a flow of lipids from the vesicle into the bilayer. This leads to the formation of a pore in the tense bilayer and fusion of the vesicle (**Fig. 1**). We are currently investigating the precise conditions under which fusion occurs, but note that the simulated fusion sequence agrees with the hypotheses underlying current models of cell fusion (Jahn and Grubmueller, 2002). The next stage in this work is to model the proteins that regulate fusion in living cells, and to explore further the complex interplay of forces that dominates the mesoscopic world of biomimetic systems.

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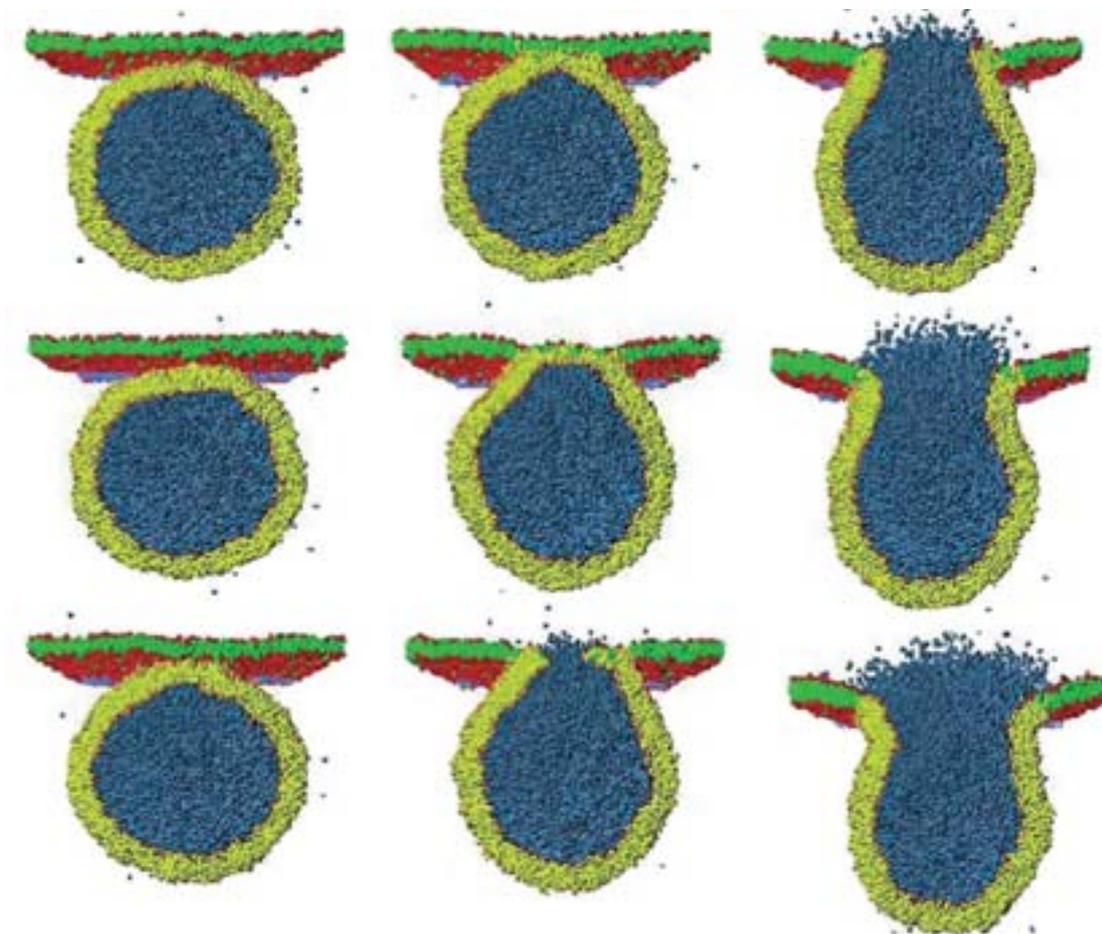


Fig. 1: Sequence of snapshots of vesicle fusion. A side view of a cut through the axis of the vesicle is shown. Water molecules exterior to the vesicle are not shown for clarity. The same lipids are used for the vesicle and planar bilayer but are colored differently for display. The vesicle diameter is approximately 50 nm and contains 6400 lipid molecules. The planar bilayer is under tension and contains 3600 lipids. The snapshots are separated by approximately 100-200 ns (not all time intervals are equal). Images produced using Pov-Ray ray tracing program: [www.povray.org](http://www.povray.org)

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# Giant Vesicles – Helping us to Understand Biological Membranes



Vesicles, or liposomes, are closed sacs made of lipid membrane encompassing fluid media. They can have sizes ranging from few tens of nanometers up to few hundreds of microns, the latter being called ‘giant vesicles’ (Fig. 1).

For the last ten years giant vesicles have been fascinating object of research for membrane scientists. Giant vesicles have the advantage of being

observable with optical microscopy. The physical characteristics of the lipid bilayer (e.g. stretching elasticity, bending stiffness, shear surface viscosity, intermonolayer slip) can be obtained from working with individual vesicles. Apart from fundamental properties of lipid membranes just mentioned above, one can study the characteristics of a multicomponent system by looking at the interactions of different molecules with the bilayer. In other words, one can bring the system closer to mimicking real cellular membranes.

One of our projects is aimed at understanding the interaction of various amphiphilic oligomers (e.g. oligooxyethylene-alkylether or C<sub>n</sub>E<sub>m</sub>) with model membranes [1]. The way we do this is by placing the membrane in a solution of molecules of interest.

A convenient technique for describing the adsorption of these molecules is Isothermal Titration Calorimetry (ITC). ITC provides a value for the strength of interaction of the molecules with the membrane (i.e. enthalpy), and the degree, to which the molecules from the bulk partition into the vesicle membrane. After adsorption, the molecules change the elasticity of the bilayer. Data for the flexibility of the membranes can be obtained by analyzing the fluctuations of vesicles [2]. Above certain concentrations, due to a drastic increase of the spontaneous curvature, C<sub>n</sub>E<sub>m</sub> induces biomimetic events such as budding of vesicles analogous to exocytosis (Fig. 2).

On the other hand, when polymers of high molecular weight, i.e., longer backbone, are anchored to the membrane, a quantitatively different effect is expected. Theoretical calculations [3] predict two regimes, mushroom and brush regime, in the dependence of the membrane stiffness on the surface concentration of anchored molecules. To verify the predictions of the model, we study membranes decorated with long  $\gamma$ -phage DNA molecules (PhD project of Vesselin Nikolov). The free end of the anchored molecule locally exerts an entropically induced pressure changing the curvature of the membrane (Fig. 3).

Bilayer composition may also lead to heterogeneous curvature due to formation of domains [4] as found in biological membranes. Lipid domains referred to as “lipid rafts” are present in the external leaflet of plasma membranes. The rafts are believed to play a significant role in cellular signal transduction. We are interested in raft formation driven by the phase behavior of lipids within the membrane. The primary objective of this study (postdoctoral project of Jeremy Pencer) is to measure the effect of membrane curvature on domain formation in vesicles composed of lipid, cholesterol and sphingolipid.

Adhesion of membranes is essential for processes like tissue formation and cellular transport.

We use vesicles on chemically structured surfaces to study adhesion (Fig. 4). Unusual morphologies and shape transitions are expected to take place in vesicles adhering to such surfaces (PhD project of Xinzhao Zhang).

We use surfaces with adhesive domains of lateral dimension in the micrometer range. Our aim is to study: (i) the effect of the domain geometry on the vesicle shapes, and (ii) morphological transitions of the adhered vesicles induced by means of change in an external parameter (e.g. osmotic pressure, temperature, surface tension).

Apart from studying adhesion of vesicles on surfaces, we are also interested in adhesion between membranes. Adhesion and fusion of membranes is essential for cellular processes like compartmentalization, import of foodstuffs and export of waste. Endo- and exocytosis involve fusion and fission of membranes. Such processes are usually triggered by external agents. An appealing approach to study these events is, first, to characterize the conditions necessary for adhesion of pure lipid membranes, and then to consider what function is to be attributed to fusogenic agents (PhD project of Christopher Haluska).

Using micromanipulation two vesicles aspirated in glass capillaries are brought together. Measurement of the contact angle between the two opposing membranes allows us to estimate the adhesion energy associated with such an event. In addition, incorporation of fusogenic agents (molecules synthesized by the group of Valerie Marchi-Artzner, College de France, Paris) which are anchored in the membrane promote fusion of the lipid bilayers. The fusogenic (sticker) molecules form complexes with trivalent metal ions in 2:1 sticker to ion ratio. When an ion binds two stickers from opposite bilayers the complex should keep the membranes close enough together for fusion to be feasible (Fig. 5).

The main barrier for fusion processes to occur is the difficulty to expel the water layer between the two adhering membranes. In our case this is overcome by the formation of metal ion complex.

Metal ions by themselves are another factor that have a significant influence on membrane functioning. Some divalent cations, e.g. Ca<sup>2+</sup>, play an important role in the regulation of biological processes such as fertilization,

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muscle contraction and signaling. Some trivalent ions were found to induce adhesion of pure lipid membranes [5]. Different salts were found to influence the solubility of proteins, so called Hofmeister effect. In some cases, the underlying mechanism causing these effects is the interaction of the ions with water: hydration, formation of water separated ion couples etc. This amounts to changing the water structure essentially by disrupting or forming hydrogen bonds. We intend to characterize the effect of different ions using ITC (PhD project of Cornelia Sinn). This technique will allow us to estimate the enthalpies associated with the mentioned above processes occurring in pure water/ions system and then compare their influence when vesicles, proteins or polymers are present in the system.

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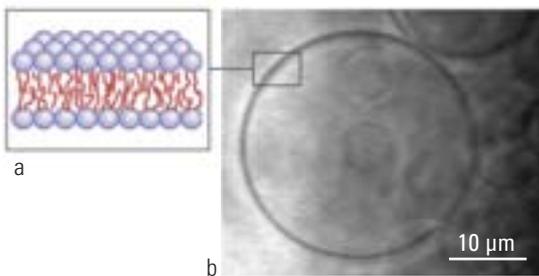


Fig. 1: a) Lipid bilayer. b) Phase contrast image of a group of giant vesicles.

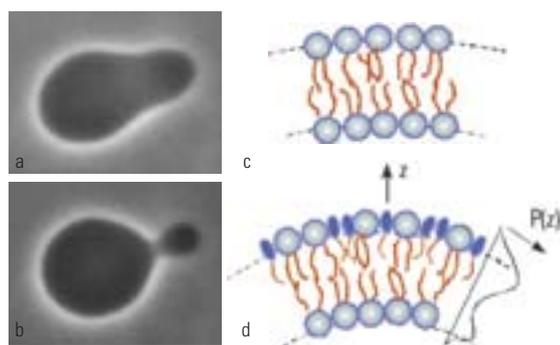


Fig. 2: a), b) Budding of a vesicle induced by adsorption of  $C_{13}E_{10}$ . c), d) Insertion of  $C_{13}E_{10}$  into the external leaflet of the vesicle membrane induces a drastic change in the bilayer spontaneous curvature.

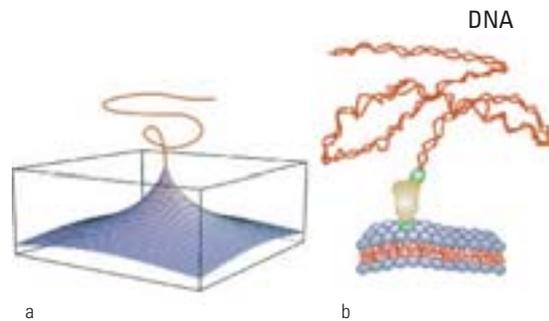


Fig. 3: a) Anchored polymer causes catenoid-like bending of the membrane (taken from [3]). b) The experimental “modeling” is done by attaching a long DNA (polymer) to a neutral lipid membrane via avidin-biotin linkage.

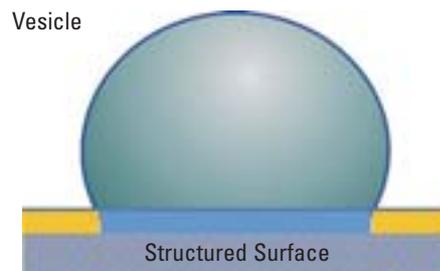


Fig. 4: Negatively charged vesicle adhering onto chemically modified glass surface. The substrate has hydrophilic positively charged domains (blue) surrounded by hydrophobic surface (yellow).

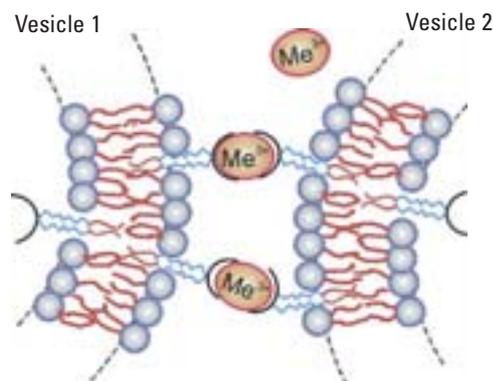


Fig. 5: Schematic presentation of two membranes brought together by sticker (or ‘fusogenic’) molecules that form complexes with trivalent metal ions.

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# New Membrane Physics with Polymersomes



Under appropriate conditions, amphiphilic molecules form bimolecular sheets in aqueous solution. Among such systems, especially lipid membranes have been of central interest for decades in biophysics due to their basic structural and functional role in living cells. Over the last 20 years, we have seen a steady growth in the number of researchers in the soft matter community working on

all aspects of membrane physics. Indeed, membranes have been one of the driving subjects of soft matter as a field [1]. Our contribution in this respect has been in the morphology of giant vesicles [2]. These are closed membrane bags with a typical size on the order of 10 micrometers.

Polymers define another flourishing area of soft matter. In particular, block copolymers have been recognized as versatile designer soft materials [3]. In aqueous solution, amphiphilic diblock copolymers form an amazing variety of morphological structures [4] on the nanometer scale. Recently, giant vesicles made from diblock copolymers, so called polymersomes, could be prepared [5], combining the active fields of polymer and membrane physics into a new promising research direction.

We have looked at the elastic and viscous properties of polymersomes made of polybutadien-b-polyethyleneoxide (PB-PEG) [6]. Just like lipid molecules, these amphiphiles self-assemble into bimolecular sheets with a thickness of a few nanometers. Whereas bending and stretching elastic properties of these novel membranes are found to fall in the range typical for lipid membranes, polymer membranes do exhibit a surface viscosity at room temperature which is about three orders of magnitude larger. Moreover, they are generally much tougher than lipid membranes; i.e., they have a higher lysis tension. They are very stable and easy to work with, which makes them interesting for biotechnological applications; e.g., they could be used for drug and gene delivery or chemical containers, in general.

In our polymersomes we find hexagonal superstructures (Fig. 1 and 2) which exhibit a high genus topology [7]. The vesicle polymer membranes swollen in sucrose/glucose solution are organized in concentric double bilayers. The interior and exterior of such a vesicle is connected by double membrane passages forming a hexagonal lattice. Note, that these passages are not holes in a single bilayer. The membrane shape is determined by the minimal bending elastic energy of the bilayer [1]. Theoretical shapes can be classified in a morphological phase diagram corresponding to the experimental shapes found (Fig. 2) [7]. It is remarkable that such superstructures form on a micrometer scale. Indeed, typical polymer morphologies were so far reported to be in the nanometer domain [3, 4]. Our finding opens a new avenue towards integration of structuring materials from small to large scales.

PB-PEG membranes exhibit a well defined thermal response, albeit with much slower time scales as lipid membranes at room temperature [6, 8]. Fig. 3 shows the typical relaxation behavior of tubular polymersomes after sudden temperature changes. The observed slow budding of polymer tubes after thermal quench is reminiscent of membrane pearling [9], which is induced by membrane tension. However, in our system, the vesicle volume and area stay constant, i.e., tension is not fixed. The morphological change can be explained in terms of a shape transition into a multi-bud configuration induced by an increase in the spontaneous curvature of the membrane [8].

The slow dynamics reflect the high membrane surface viscosity [6], which leads to internal rather than hydrodynamic dissipation. Thus, dynamic correlation functions of thermal shape fluctuations exhibit new interesting scaling behavior.

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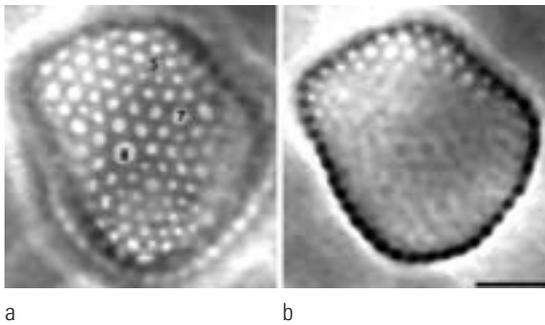


Fig 1: High genus polymersome. The top view (a) shows an optical phase contrast micrograph of a typical hexagonal lattice of passages in a double bilayer vesicle surface. Note the  $n$ -fold defects in the hexagonal lattice. The cross section (b) of the same polymer vesicle shows nearly circular tubes forming the double bilayer surface. The scale bar corresponds to  $10\ \mu\text{m}$ . Figure taken from [7].

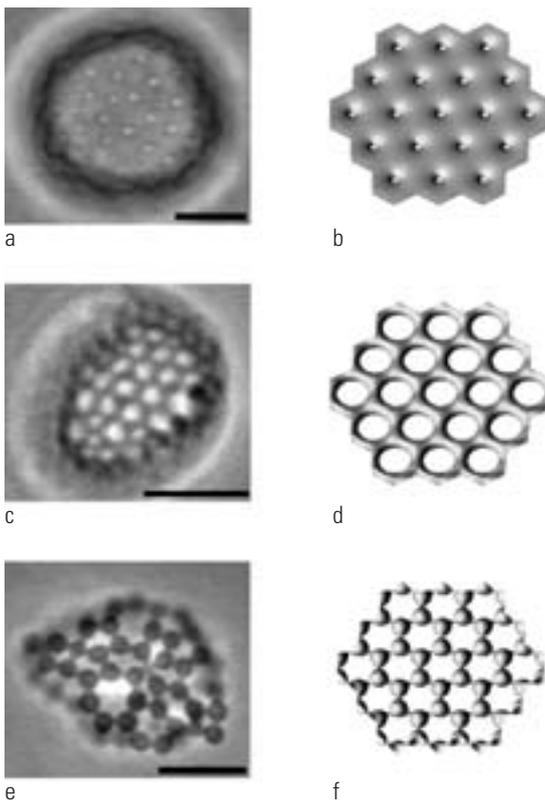


Fig 2: Comparison of experimental and theoretical lattice shape classes. The scale bar corresponds to  $10\ \mu\text{m}$ . Theoretical shapes were obtained via direct minimization of membrane bending energy. Figure adapted from [7] connected by double membrane passages forming a hexagonal lattice.

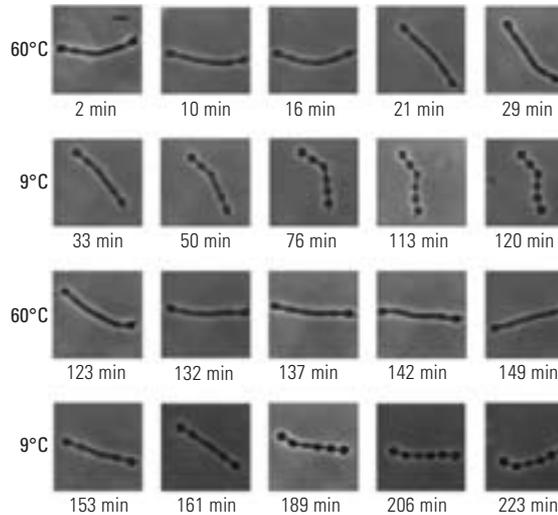


Fig 3: Reversible budding of tubular polymersomes induced by thermal cycling between  $9$  and  $60\ ^\circ\text{C}$ . Snapshots were obtained at times noted below each frame. Figure taken from [8].

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# Emmy Noether Junior Research Group



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The main interest of our group is the role which material properties play for the functioning of biological cells. In particular, we are interested in the role of forces and elasticity in cell adhesion. Other interests of our group relate to the theoretical understanding of biomaterials. For example, we investigate the structural properties of spatially extended structures in lipid-water mixtures.

## Forces and Elasticity in Cell Adhesion

It is well known, especially in the medical community, that mechanical input is essential for proper functioning of certain cell types, including tissue cells from bone, lung and blood vessels (which under physiological conditions are subject to permanent strain through body movements, breathing and blood pulsation, respectively). During the last year, there has been a large effort to clarify the underlying mechanisms on the level of single cells. It is now clear that most adherent cells not only react to external force in a specific way, but also that cells actively exert force on their environment in order to probe its mechanical properties (active mechanosensing).

For cells adhering to extracellular matrix, the force transmitting sites of adhesions are the so-called focal adhesions. In collaboration with cell biologists at the Weizmann Institute in Israel, we were able to show that internally generated force and lateral size of focal adhesion correlate in a linear way, with a stress constant of  $5.5 \text{ nN}/\mu\text{m}^2$  [1]. For this study, we developed a new technique to reconstruct forces at single focal adhesions from the deformations of a micro-patterned elastic substrate, namely by numerically solving the ill-posed inverse problem of linear elasticity theory [2]. **Fig. 1** shows the reconstructed forces exerted by a fibroblast at fluorescently labeled focal adhesions.

Since elastic deformations are long-ranged and sensitively depend on boundary conditions of the surrounding medium, cells might sense external perturbations, mechanical activity of other cells or geometrical features like boundaries through local mechanosensing. Using defect theory and linear elasticity theory, we developed several models for cell organization in soft media [3, 4]. Force patterns of polarized cells are typically pinch-like and can be modeled as anisotropic force contraction dipoles. The surrounding medium is assumed to behave like an isotropic elastic medium, which applies to many synthetic elastic substrates and which is expected to be a good approximation for hydrogels on large time and length scales. For the cellular reaction to strain, in one model we assumed that the cells react like inert physical particles [3]. This case might apply to artificial cells with a contractile system but without biochemical regulation. We found that cellular structure formation is similar

to the case of electric quadrupoles, with neighboring cells orienting perpendicular to each other. In order to model the behavior of cells with regulated response, we started from the observation that growth of focal adhesions might be triggered by a threshold in force. Since build-up of force is more efficient in a stiff environment, we suggested that cell processes are favored which proceed in a direction of large effective stiffness [4]. We found that in this case, cells line up in strings, exactly as observed experimentally. In regard to boundary effects, we were able to show that cells align perpendicular and parallel to clamped and free boundaries, respectively, again in excellent agreement with experimental observations (**Fig. 2**).

## Cubic Phases in Lipid-Water Mixtures

Different ordered phases are known to form in lipid-water mixtures, including lamellar, hexagonal and cubic bicontinuous phases. The cubic phases have been found to form in many membrane-rich regions of cells and are used for crystallization of membrane proteins. In a bicontinuous structure, one highly convoluted interface spans the whole sample, thereby dividing it into two separate labyrinths [5]. Since surfaces with vanishing mean curvature (minimal surfaces) minimize the bending energy of lipid bilayers, triply periodic minimal surfaces are the main structural models for ordered bicontinuous phases in lipid-water mixtures. Here the mid-surface of the lipid bilayers corresponds to the minimal surface, while the neutral surfaces of the two lipid monolayers correspond to parallel surfaces to the minimal surface (**Fig. 3**).

Although there are a large number of different cubic minimal surfaces, in lipid-water mixtures only the structures G, D, P and I-WP have been identified experimentally [5]. In our theoretical work, we showed that phase behavior is determined by the distribution of Gaussian curvature over the minimal mid-surface. In detail, we found that the relative stability of the different cubic phases is determined by the dimensionless quantity  $\Delta$ , which characterizes the width of this distribution [6, 7]. G, D and P have the same small value of  $\Delta$  because they belong to the same Bonnet family. I-WP has a larger value and thus needs stabilization through additional physical mechanisms to become stable. All other structures have even larger values, which explain why they are not observed in experiments. Moreover, we found that the sequence of phases with increasing water content is determined by the dimensionless topology index, which describes the porosity of the structure. This explains the generic sequence G – D – P found in experiments when increasing water content.

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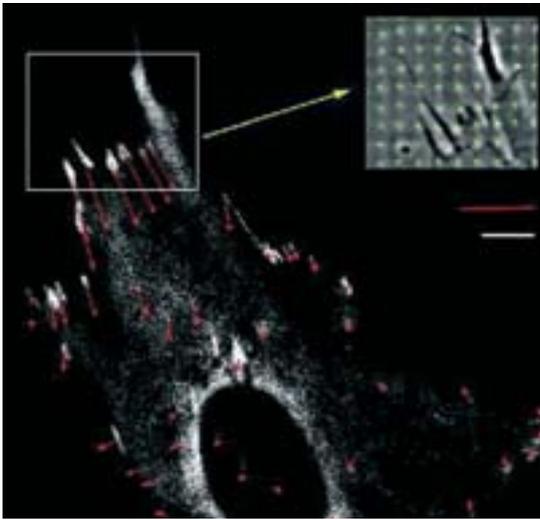


Fig. 1: Forces (red) exerted by an adhering fibroblast at sites of focal adhesions (white) which are fluorescently labeled. The inset shows a phase contrast image of the deformation of the micro-patterned elastic substrate (green), from which the force pattern has been calculated. White bar = 4  $\mu\text{m}$ , red bar = 30 nN.

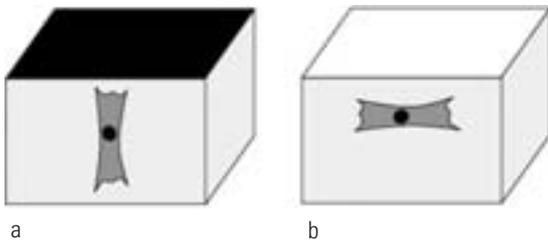


Fig. 2: Mechanically active cells in soft media align (a) perpendicular to clamped boundaries and (b) parallel to free boundaries, because in this way, they sense an effective increase in stiffness, which is favorable for growth of focal adhesions.

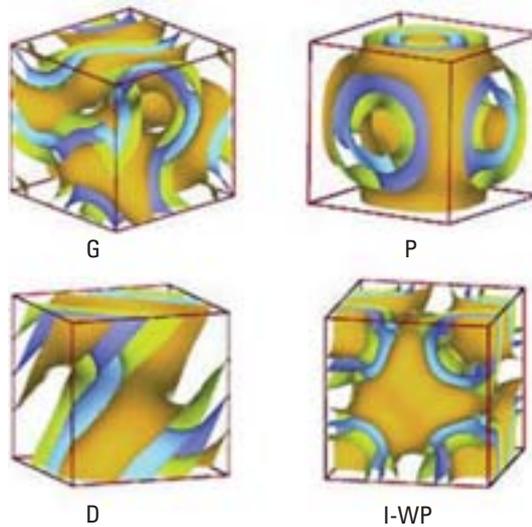


Fig. 3: Models for cubic bicontinuous phases in lipid-water mixtures: the mid-surface of the lipid bilayer is a triply periodic minimal surface (blue). The two parallel surfaces are the neutral surfaces of the lipid monolayers (orange).

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# Adhesion Behavior of Vesicles at Finite Temperature



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Biological cells are the fundamental building blocks of living organisms. The investigation of cell properties is essential for the principal understanding of life species as well as for the progress of medical technology in fields like cancer therapy or the development of more effective drugs and drug delivery methods, to name just two application areas.

A biological cell is surrounded by a closed membrane surface that serves as an interface to the outside world. The membrane is typically fluid and may consist of various components. The bending rigidity of the membrane and the molecular interaction with external substances have an important influence on the cell morphology and the cell's adhesion behavior. The adhesion of a cell to an external substrate is of special interest with respect to implantation technology.

In many cases cells act very similar to vesicles, which are homogeneously filled membrane shells. Vesicles serve as simple, well determined model systems of cells. This text describes a simulation based analysis of the adhesion of vesicles [1].

In the simplest case a vesicle membrane is a one-component double layer of identical lipids.

The membrane area can be assumed to be almost incompressible. Then, the membrane material can be characterized by its bending rigidity  $\kappa$  and the spontaneous curvature  $C_0$  only. Molecules larger than water have an extremely low probability to permeate the membrane, so that concentration gradients across the membrane lead to an osmotic pressure  $P_{os}=T(n_{in}-n_{out})$ . If (in and outside of the vesicle) there is a high concentration  $n$  of sugar molecules the vesicle volume is almost fixed at a value for which  $n_{in}=n_{out}$ . If the concentration is very low, the osmotic pressure can be neglected.

We consider the low concentration scenario and exclude any spontaneous curvature,  $C_0=0$ . Then, the behavior of a free vesicle is solely determined by the bending rigidity.

The higher the bending rigidity  $\kappa$  of the vesicle is, the more it resembles a sphere, which is the global minimum shape with respect to the elastic energy. Entropic fluctuations result for lower  $\kappa$  in a more flaccid and oscillatory surface membrane.

A vesicle close to a solid substrate may be exposed to sundry attractive and repulsive forces [2]. In any case two important forces (Fig. 1) are always present:

- The attractive van-der-Waals force between the lipid heads and the substrate atoms;
- An effective, fluctuation induced force which is repulsive and arises from the entropy based collisions of the fluctuating membrane against the substrate.

For a membrane in front of a hard wall the potential  $V_H$  of the fluctuation induced force is proportional to  $V_H \sim T^2/\kappa z^2$ , where  $z$  is the distance to the wall.

The adhesion behavior of the vesicle is influenced by the bending rigidity in the following way: An adhered vesicle with a high  $\kappa$  has almost the shape of a sphere, and so the contact area is almost zero.

For lower  $\kappa$  the global shape of the vesicle changes such that the contact area, i.e. the amount of membrane matter within reach of the attractive substrate potential, increases [3]. Consequently, the total negative adhesion energy decreases; at the same time the repulsive fluctuation induced force increases (Fig. 2, Fig. 3). For large  $\kappa$  the fluctuations are of minor importance. For small  $\kappa$  the contact area is bounded by its maximum (which is half of the total membrane area) while the fluctuating force increases like  $\kappa^{-1}$ . Thus, there should be a certain  $\kappa$  in between at which the adhesion energy is minimum. Indeed, such a minimum could be found.

With the help of Monte-Carlo simulations the behavior of a one-component vesicle adhered to a substrate was investigated. The simulations allow a study of the average adhesion behavior of a membrane in the canonical ensemble.

The vesicle membrane was treated as a smooth closed surface that was mimicked by a flexible triangulation. The mechanical properties of the membrane were resembled by a discretized elastic energy and the tethered beads model [4]. For the interaction with the wall a (10,4)-Lennard-Jones potential was used. The substrate was taken to be smooth and parallel to the  $z=0$ -plane.

The Plot in Fig. 4 shows the average adhesion energy of a vesicle as a function of its bending rigidity. In accordance with the considerations above, the plot has a minimum. Left of the minimum  $\kappa \approx 3$  the adhesion energy  $E_{wall}$  is dominated by fluctuation based forces. For  $\kappa > 3$  the decrease of the contact zone is responsible for the increase of  $E_{wall}$ .

The plot in Fig. 5 gives a deeper insight into the system. For this plot the space in front of the substrate is divided into layers of distance  $(z, z+dz]$ .

The plot shows the amount  $\rho_m(z)$  of membrane matter that lies within each of these layers, i.e. the lipid density integrated over  $x$  and  $y$ .

The separation from the substrate is given in units of the distance  $z_{min}$ , the distance where the Lennard-Jones potential is minimum. The plot focuses only on the important part of the vesicle close to the wall. In fact,  $\rho_m(z)$  does not become zero up to values of  $z=15 z_{min}$  and higher, far out of the region shown in Fig. 5. The amount of membrane matter in the region near the wall increases with decreasing  $\kappa$  corresponding to an increase of the contact area. At the same time the density distribution gets broader which indicates an increase of fluctuations. Finally, for  $\kappa=2kT$  the total amount of matter in the observed region is larger than that for  $\kappa=7.5kT$  but it is distinctly more spread out, and the peak at  $z_{min}$  is lower than the peak for  $\kappa=7.5kT$ . This means, for entropic reasons parts of the membrane in the contact area are pushed away from the optimum distance from the wall.

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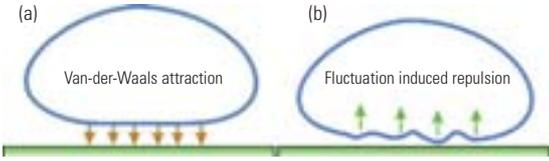


Fig. 1: Adhered vesicles are exposed to (a) van-der-Waals attraction and (b) effective repulsion induced by fluctuations.

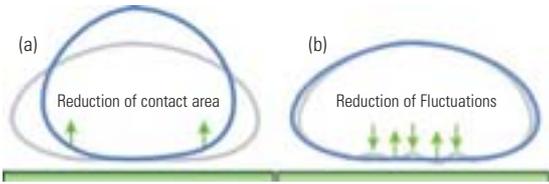
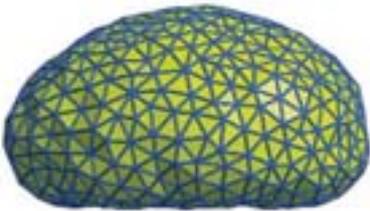


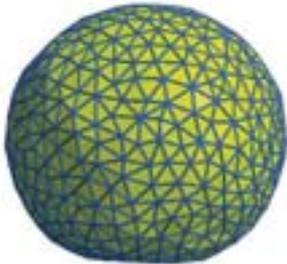
Fig. 2: If  $\kappa$  is increased, (a) the contact area shrinks, (b) the fluctuations are reduced.



(a)



(b)



(c)

Fig. 3: Snapshots of adhered vesicles with (a)  $\kappa=3kT$ , (b)  $\kappa=15kT$ , (c)  $\kappa=40kT$

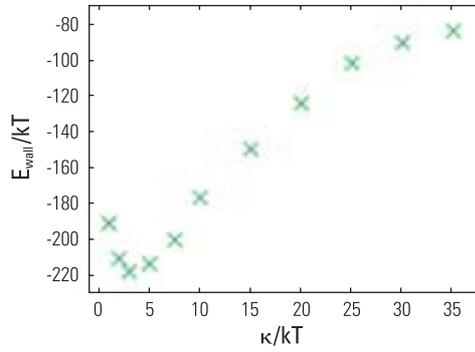


Fig. 4: Adhesion energy of an adhered vesicle as a function of the bending rigidity.

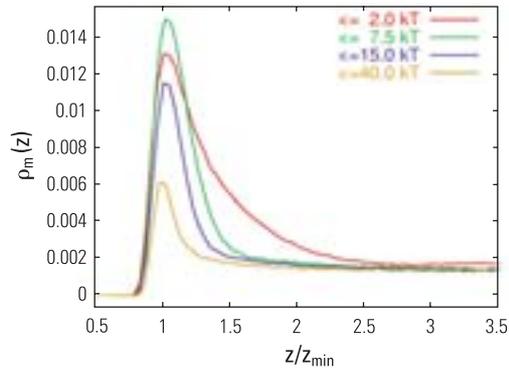


Fig. 5: Amount of membrane matter  $\rho_m(z)$  in layers of distance  $z$  from the substrate

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# Membrane Adhesion



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The adhesion of cells plays a key role in important biological processes such as tissue development and immune response. The highly selective interactions leading to cell adhesion are mediated by a variety of specific receptors which are embedded in the cell membranes. The bound receptor-ligand pairs of opposing cells are often arranged into supramolecular patterns which show a complex evolution during cell adhesion. For some biological processes, the formation of these patterns seems to be a central event in cell activation. For example, the immune response of T lymphocyte and natural killer cells to target cells is triggered by the formation of characteristic patterns at the cell-cell junction.

We have developed a statistical mechanical model for the adhesion of multicomponent membranes with adhesive receptors (stickers) and repulsive macromolecules (repellers). The repellers mimic the glycocalyx of the cell, imposing a steric barrier for the adhesion. This barrier strongly affects the equilibrium phase behavior and the adhesion dynamics of the membrane. The unbinding transition is continuous for weak barriers, and discontinuous for strong barriers [1, 2].

To model the adhesion dynamics of a cell, we consider a membrane consisting of a circular contact area surrounded by nonadhering area in which the membrane is not in contact with the second membrane [3]. We find distinct dynamic regimes of pattern formation depending on the characteristic lengths and the concentrations of stickers and repellers: (A) Long repellers impose a strong barrier to sticker adhesion. The nucleation time for sticker binding therefore is large compared to typical diffusion times, and the membrane binds via growth of a single sticker nucleus; (B) For short repellers, the nucleation time for sticker binding is small, and many nuclei of bound stickers are formed initially. Due to the diffusion of stickers into the contact area, nuclei at the rim of this area grow faster, and at sufficiently high sticker concentrations, a ring of bound stickers is formed which encloses a central domain of repellers, see Fig. 1 below. At later times, this pattern inverts, and a central sticker cluster is surrounded by repellers. The sequence of patterns in this regime has a striking similarity to the pattern evolution observed during T cell adhesion; (C) In an intermediate regime, the sticker concentration is not large enough for the formation of a closed sticker ring from the initial nuclei. Instead, circular arrangements of separate sticker clusters emerge.

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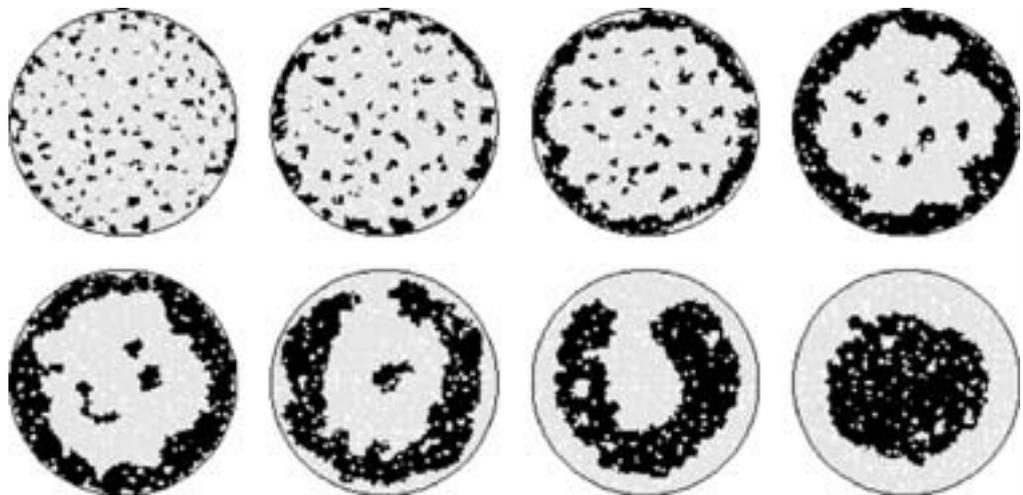


Fig. 1: Time sequence of MC configurations for the contact area. Stickers are shown in black, repellers in grey. Due to the diffusion of stickers into the contact area, clusters at the rim grow faster, forming rings at intermediate time scales. The final configuration represents the equilibrium state.

# Protein Folding Kinetics

What are the rates and routes of folding of 2-state proteins? 2-state proteins are relatively small proteins that fold and unfold with single-exponential kinetics, and so can be modeled in mass-action kinetics using only two states, D (denatured) and N (native). An important recent observation is the correlation found by Plaxco et al. [1] between the folding rates of 2-state proteins and the 'topology' of their three-dimensional structures. Plaxco et al. quantified the topology by the average contact order (CO), the average sequence separation  $|i-j|$  between all monomers  $i$  and  $j$  in contact in the folded structure. Proteins with predominantly local contacts have a small average CO (e.g.,  $\alpha$ -helical proteins) and fold faster than proteins with many nonlocal contacts having a larger average CO (e.g.,  $\beta$ -proteins).

We have developed a simple model to calculate the folding rates and routes of 2-state proteins from the contact maps of their three-dimensional structures [2,3]. The model is based on the graph-theoretical concept of effective contact order (ECO). The ECO is the length of the loop that closes to form a contact between two monomers, for a chain with a given set of contacts. More precisely, the ECO is the number of steps along the shortest path on the polymer graph between two monomers  $i$  and  $j$  for a chain in a given configuration. While the CO is independent of the folding path, the ECO is dependent on the folding routes and therefore gives information about the mechanism of folding.

We find that proteins fold in general along opportunistic zipping routes in which each step in folding involves only a small loss of conformational entropy. The ECO provides a way to calculate this conditional conformational entropy loss for each zipping step. In short, while there are many routes that a protein can follow to lower its energy, we find that only a very small fraction of those routes are low-entropy-loss routes, and hence are predicted to be the dominant folding routes.

An example is shown in Fig. 1. The three-dimensional structure of the Chymotrypsin Inhibitor 2 (CI2) consists of a four-stranded  $\beta$ -sheet packed against an  $\alpha$ -helix. The contact map of CI2 has four major contact clusters corresponding to the  $\alpha$ -helix and the  $\beta$ -strand pairings  $\beta_2\beta_3$ ,  $\beta_3\beta_4$ , and  $\beta_1\beta_4$ . The strand pairing  $\beta_1\beta_4$  involves highly nonlocal contacts between the two ends of the chain, and therefore turns out to be the folding bottleneck. However, we find that only a relatively small loop has to be closed if  $\beta_1\beta_4$  folds after the other three major clusters  $\alpha$ ,  $\beta_2\beta_3$ , and  $\beta_3\beta_4$ . On this dominant low-entropy-loss route, all major clusters are involved in the rate-limiting bottleneck, the formation of the  $\beta_1\beta_4$  strand pairing. Therefore, this route rationalizes the experimental observation that mutations along the whole protein chain affect the folding rate of CI2.

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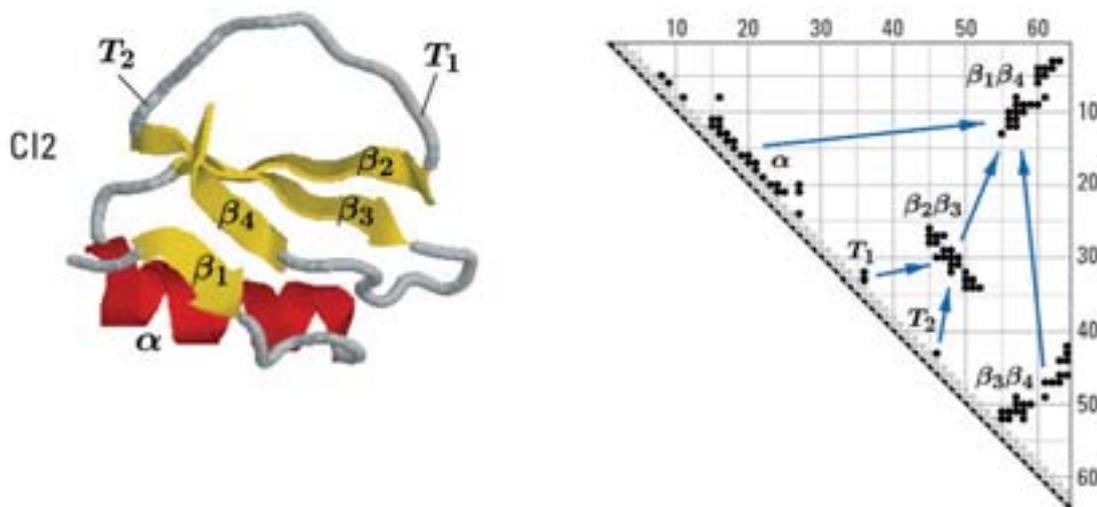


Fig. 1: Left: Structure of the Chymotrypsin Inhibitor 2 (CI2). --- Right: Contact map with dominant folding route for CI2.

# Polyelectrolytes



## Annealed Polyelectrolytes

'Weak' polyelectrolytes as, e.g., poly(acrylic acid) dissociate in a limited pH range. The average degree of dissociation  $\langle f \rangle$  is determined by the pH of the solution which, in physical terms, corresponds to the chemical potential  $\mu$  of the charges. Because the total number of charges as well as their positions along the chain are fluctuating, such polymers are also called 'annealed' polyelectrolytes.

**Θ and good solvent:** A charge accumulation appears at the chain ends within a size of the order of the screening length  $\lambda_D$ . The equilibrium charge distribution  $f(s)$  on a flexible chain was given in ref. [1]. To check the theoretical prediction we started with a simulation model chosen as close as possible to that used in theory where the charges are assumed to interact by a screened Coulomb potential. We study annealed polyelectrolytes by semi-grand canonical Monte Carlo simulations where the chain is in contact with a reservoir of charges of fixed chemical potential  $\mu$ . **Fig. 1** shows the charge distribution obtained in simulations together with the theoretical prediction. In a fairly wide parameter range, we observe almost perfect agreement [2].

**Poor solvent:** Additionally to the model used for  $\Theta$  solvents, a short-ranged attractive potential is included. To scan properly the phase space in the case of globular structures, additional kinds of Monte Carlo moves are added. Polyelectrolytes in poor solvent are known to be unstable to the so-called pearl-necklace conformation. For annealed polyelectrolytes, however, the pearl-necklace structure itself becomes unstable if the solvent is too poor. (The solvent quality is measured by the normalized distance from the  $\Theta$  point  $\tau$ .) Upon increasing the charge, the polyelectrolytes are expected to show a discontinuous transition between a collapsed globular conformation and a stretched one. In the simulations this transition is seen in a quite large parameter range (**Fig. 2**) [3]. Only in a rather limited region, in particular at small Bjerrum lengths  $\lambda_B$ , we obtain pearl-necklaces. In **Fig. 3** a dumbbell-like structure is shown.

## Polyelectrolyte Brushes

Polymer brushes are systems in which chains are attached by one end to a surface in a way that the grafting density is high enough to enforce stretching of the chains away from the surface resulting in a brush-like conformation. Polyelectrolyte brushes constitute a new class of materials which has recently received considerable interest. Here we report two novel brush regimes first obtained by simulation studies on polyelectrolyte brushes. The new features not predicted by previous theories stimulated a better theoretical understanding of this class of polymers.

**Collapsed brush regime:** At moderate interaction strength  $\lambda_B=0.7b$  we observe a new collapsed regime where the monomer density becomes independent of the grafting density resulting in a linear scaling of the brush height with  $\rho_a$  [4] (**Fig. 4**). Including electrostatic correlations, which cause an attractive interaction, the nature of the collapsed regime can be understood within an extended scaling model [5]. The resulting phase diagram is shown in **Fig. 5**. The brush can collapse at strong coupling  $\lambda_B^3 > v_2$  and strong charging  $f > (v_2/\lambda_B^3)^{1/2}$ , with  $v_2$  being the second virial. In this phase, the brush height, resulting from a balance between steric repulsion and attractive Coulomb correlations, grows indeed linearly with  $\rho_a$ .

**Non-linear osmotic brush regime:** Reducing  $\lambda_B$  the collapsed brush regime disappears [6] as predicted by the extended scaling theory [5]. However, contrary to the scaling law of the osmotic regime, the brush height exhibits still a weak dependence on  $\rho_a$  (**Fig. 4**). Such a behavior is known to appear if the counter ion distribution extends substantially beyond the rim of the brush. Obviously, this does not happen in our case (**Fig. 4**). In all previous theoretical models it was assumed that counter ions are distributed uniformly in the lateral directions. However, inhomogeneous distributions were obtained both in experiment and simulation. Recently it has been shown that lateral inhomogeneity indeed yields a weak dependence of brush height on anchoring density [7]. The corresponding brush regime is called non-linear osmotic. In **Fig. 6** we compare simulation results with theoretical predictions obtained without any fitting parameter. Within the order of the systematic error of the model we find reasonable agreement.

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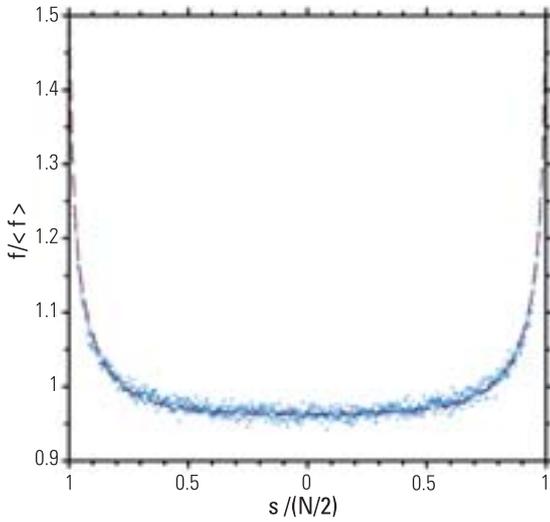


Fig. 1: Charge distribution on a Gaussian chain ( $N=1000$ ,  $\langle f \rangle=0.083$ ,  $\lambda_D=64b$ ). Theoretical results are given as dashed line, simulation data as dots.

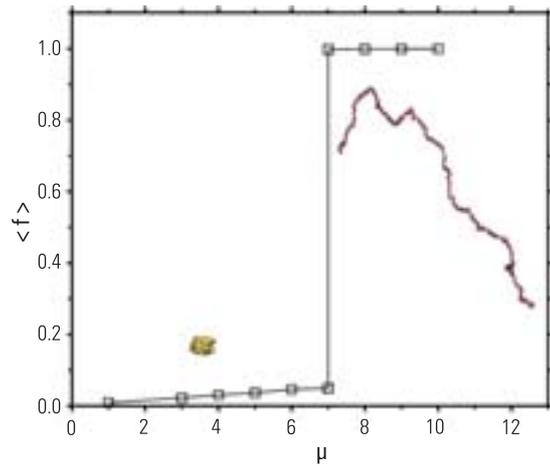


Fig. 2: Average degree of charging versus chemical potential (titration curve) for a chain of length  $N=256$  at  $\tau=0.22$ ,  $\lambda_B/b=1$ . The conformations are indicated by typical snapshots (charged monomers are colored red, uncharged ones yellow).

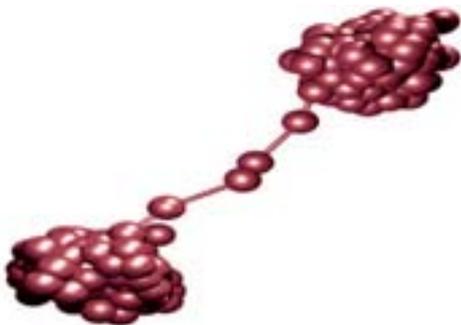


Fig. 3: Snapshot of a chain with  $N=256$  monomers at  $\tau=0.22$ ,  $\lambda_B/b=0.01$ ,  $\mu=6.0$ . Note that inside the pearls there are a few uncharged monomers.

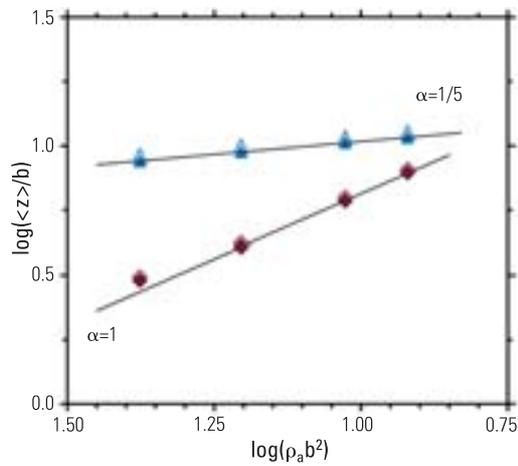


Fig. 4: Average brush height (filled symbols) and height of counterion layer (open symbols) versus grafting density. Completely charged brushes at  $\lambda_B=0.7b$  (diamonds) and  $\lambda_B=0.1b$  (triangles). The lines give power laws  $\langle z \rangle \sim \rho_a^\alpha$ .

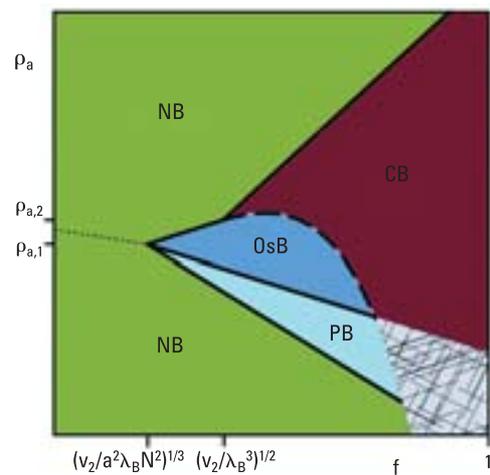


Fig. 5: Scaling theory phase diagram in logarithmic scales with quasi-neutral (NB), osmotic (OsB), Pincus (PB) and collapsed (CB) brush regimes.

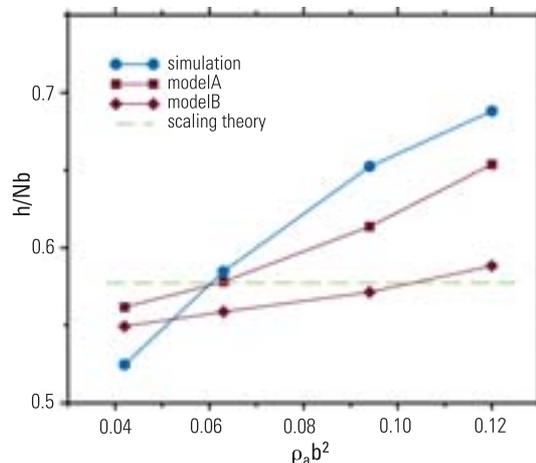


Fig. 6: Brush height versus grafting density at  $\lambda_B=0.1b$ ,  $f=1$ . Simulation data and theoretical predictions

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# Semiflexible Polymers and Filaments



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Many biopolymers such as DNA, filamentous (F-) actin or microtubules belong to the class of semiflexible polymers. The biological function of these polymers requires considerable mechanical rigidity. For example, actin filaments are the main structural element of the cytoskeleton which gives the cell unique mechanical properties as it forms a network rigid enough to maintain the shape of the cell and transmit forces yet flexible enough to allow for cell motion and internal reorganization as response to external mechanical stimuli.

The physics of semiflexible polymers is in many respects fundamentally different from the physics of flexible synthetic polymers such as polyethylene.

For semiflexible polymers not only the conformational entropy but also the bending energy plays an important role. The bending stiffness is characterized by the persistence length. On scales larger than the persistence length the polymer loses its orientation and starts to behave as flexible, mostly entropic chain whereas on smaller scales bending energy dominates and qualitatively new semiflexible behavior appears. The persistence lengths of the most prominent biopolymers range from 50 nm for DNA to the 10  $\mu\text{m}$ -range for F-actin or even up to the mm-range for microtubules and are thus comparable to typical contour lengths the polymers such that semiflexible behavior plays an important role.

Another important class of semiflexible polymers are polyelectrolytes where the electrostatic repulsion of charges along the backbone can give rise to considerable bending rigidity depending on the salinity of the surrounding solution.

Semiflexibility is also crucial for the bundling of two such biopolymers by attractive interactions as well as their adsorption onto adhesive substrates as shown schematically in **Fig. 1**. Unbundling and desorption transitions are due to the competition between the energy gained by binding to an attractive potential well and the associated loss of configurational entropy. As the bending rigidity and, thus, the persistence length is increased the entropy loss is reduced. Therefore semiflexible polymers bundle and adsorb more easily as compared to a flexible polymer.

These problems can be theoretically described as single polymer problems in the presence of an external binding or adsorbing potential. Intermolecular forces give rise to polymer/polymer or polymer/surface interactions that contain both an attractive potential well and a repulsive hard core, see **Fig. 2**. However, attraction might also depend on the orientation of polymer segments, for example, if the binding is mediated by crosslinkers.

We have studied this problem analytically solving the differential transfer matrix equation **[1]**. The transfer matrix calculation allows to obtain explicit expressions for the transition points, the order of the unbundling and desorption transition, and the critical exponents which characterize the corresponding critical behavior. Results for the critical exponents agree with renormalization group results **[2]**. The transfer matrix approach identifies up to four distinct universality classes corresponding to the four interaction potentials shown in **Fig. 2**. Somewhat surprisingly, it turns out that the orientation dependence of the attraction can influence the order of these transitions which is a distinct feature of semiflexible polymers. In 1+1 dimensions the transfer matrix approach even allows to calculate the exact distribution of polymer segment positions and orientations. We also find that the repulsive hard core part of the interaction potential becomes irrelevant in higher dimensions  $d \geq 3$ . All analytical results have been confirmed by numerical transfer matrix calculation and Monte-Carlo simulations, a snapshot of which is shown in **Fig. 3**.

Desorption does not only occur as a result of increasing temperature and thermal fluctuations but also if a desorbing force is applied to one end of the polymer, as indicated in **Fig. 3**. This force-induced desorption can be experimentally studied using single molecule AFM techniques. Using the exact transfer matrix result for the probability distribution of polymer segments the force-extensions characteristics for desorption by an applied force can be obtained. One interesting feature is the occurrence of an energetic barrier against force-induced desorption which is solely due to the effects from bending rigidity.

A bundle of three attractive semiflexible polymers (**Fig. 4**) represents a more challenging problem that can only be studied by scaling arguments and extensive Monte-Carlo simulations **[3]**. One basic question regarding bundles of more than two polymers is whether the bundling proceeds via a sequence of transitions in pairs or in a single cooperative transition. Surprisingly it turns out that the phase transition is cooperative, similar to what is shown in **Fig. 5** for identical persistence lengths, even for a wide range of different persistence lengths.

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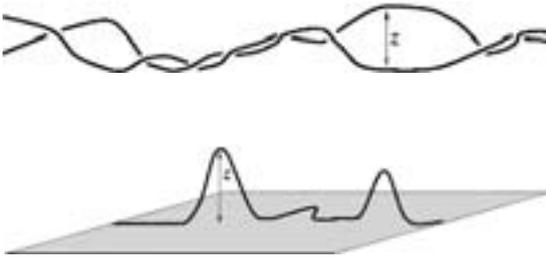


Fig. 1: Top: Bundling of two semiflexible polymers.  
Bottom: Adsorption of a semiflexible polymer onto a planar substrate.



Fig. 4: Snapshot of a Monte-Carlo simulation of a bundle of three semiflexible polymers.

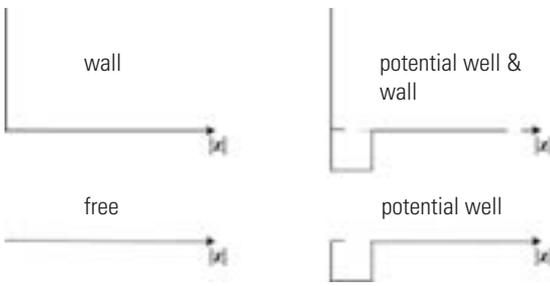


Fig. 2: Four types of interaction potentials corresponding to the four different universality classes.



Fig. 3: Snapshot of a Monte-Carlo simulation of an adsorbed polymer. A force applied to one polymer end (arrow) can lead to force-induced desorption.

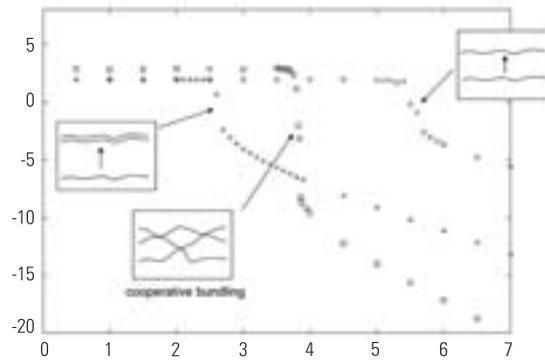


Fig. 5: Potential energy of three identical semiflexible polymers as function of attraction strength in 1+2 dimensions. The discontinuity signals the location of a (first order) bundling transition. Two subsequent transitions in pairs would give the curves on the right (circles) and on the left (triangles). The Monte-Carlo simulation shows that the actual transition is cooperative and happens along the curve in the middle (squares) before the first pair can bind.

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# Molecular Motors and Active Systems



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Our current understanding of the movements of molecular motors is based on biomimetic models systems. Prominent examples are cytoskeletal filaments such as microtubules which are immobilized onto solid substrates and which interact with mobile motor molecules such as kinesin, compare **Fig. 1**. These motors are powered by the free energy released from the exergonic hydrolysis of adenosine triphosphate (ATP). In fact, these motors are able to transform the free energy released from the hydrolysis of a single ATP molecule into mechanical work. Thus, these motors use the smallest possible amount of fuel. One such motor is kinesin, as shown in **Fig. 1**, which walks along microtubules.

This motor is observed to walk via discrete steps, the size of which is close to the repeat distance of the filament which is 8 nm. At each step, the cytoskeletal motor has a small but nonzero probability to unbind from the filament. Thus, it makes of the order of a hundreds steps before it falls off.

On larger time scales, the motor undergoes peculiar random walks which consist of alternating sequences of bound and unbound motor states, i.e., of directed walks along the filaments and nondirected diffusion in the aqueous solution.

## Active Transport

In our theoretical work, the directed walks of bound motors are studied in the framework of stochastic ratchet models which are mapped onto discrete networks as shown in **Fig. 2**. These networks can have an arbitrary number of vertices but are periodic in one spatial direction which corresponds to the motor displacement parallel to the filament.

A detailed analysis of the stochastic networks reveals that they exhibit universal features. One such feature is the functional relationship between the motor velocity and the concentration of the fuel molecules. This functional dependence is primarily determined by the total number  $Q$  of unbalanced transitions present in the network. If the unbalanced transition rates obey Michaelis-Menten kinetics, one obtains general functional relationships for the motor velocity  $v_b$  on the concentration  $\Gamma$  of the fuel molecules and on the external force  $F$  as given by **[1, 2]**

$$v_b(\Gamma, F) = \left[ \sum_{n=0}^Q g_n(F) \Gamma^n \right] / \left[ \sum_{n=0}^Q h_n(F) \Gamma^n \right] \quad (1)$$

Thus, the velocity  $v_b$  can be expressed in terms of the ratio of two  $\Gamma$ -polynomials of degree  $Q$  with  $F$ -dependent coefficients.

In this way, one arrives at a classification scheme for the functional dependence of the velocity on the two parameters  $\Gamma$  and  $F$  which agrees, for  $Q=1$ , with the experimental observations on kinesin. For each value of  $Q$ , the functional relationships as given by (1) are universal in the sense that they are valid (i) for any number of balanced transition rates, (ii) for any choice of the molecular force potentials, (iii) for arbitrary load force  $F$ , and (iv) for any force dependence of the Michaelis-Menten reaction rate constants.

## Active Pattern Formation

As mentioned, the motor unbinds from the filament after a certain walking time and then undergoes peculiar random walks. A particularly interesting system, in which one can study these walks, is provided by a filament which is immobilized within a tube-like compartment as shown in **Fig. 3**. This system resembles an axon and corresponds to a finite concentration of motors in a closed tube.

In the presence of ATP, the motors move to the right (plus end of filament). As a result of this directed motion, a density gradient builds up which acts to create a diffusive backflow of unbound motors towards the left. This leads to a stationary state characterized by a nonuniform density profile for which the right part of the filament exhibits a traffic jam. These nonuniform density profiles represent simple examples for active pattern formation. **[3]**

In the stationary state, the bound and the unbound currents cancel each other. If one now studies the bound current as a function of the overall motor concentration, one finds that this quantity exhibits a maximum which reflects the presence of traffic jams for larger concentrations.

## Active Transformations

In general, an active system may exhibit more than one stationary state and may then undergo active transformations between these different states. One example for such active transformations is provided by open tube-like compartments for which the two ends are coupled to motor reservoirs with certain motor densities. As one varies these boundary densities, the system can undergo active transformations between a high-density, a low-density, and a maximal current state. **[4]**

More recently, we have found that phase transformations are also present for closed tube-like compartments which contain two different types of motors.

The concepts of active transport, active pattern formation, and active transformations are quite general and apply to a wide range of biomimetic systems with active components.

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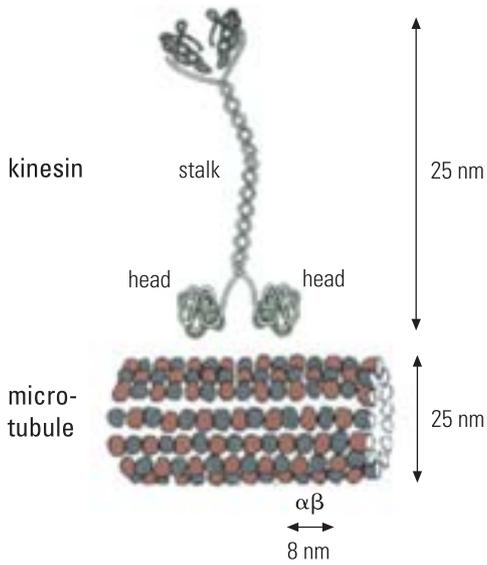


Fig. 1: The molecular motor kinesin has two motor domains or heads which can both bind to the microtubule and hydrolyse ATP.

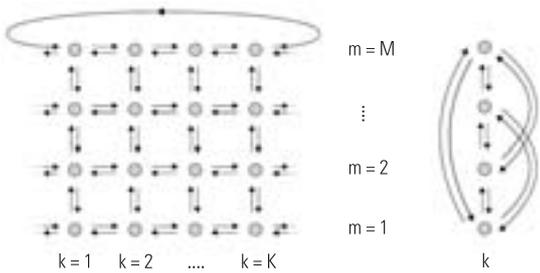


Fig. 2: Stochastic network of KM discrete motor states represented by vertices  $(k, m)$  with  $1 \leq k \leq K$  and  $1 \leq m \leq M$ . The arrows or directed edges correspond to transitions between these states (left). The network satisfies periodic boundary conditions in the longitudinal direction parallel to the  $k$ -axis; and (right) it has an arbitrary number of transverse dimensions.

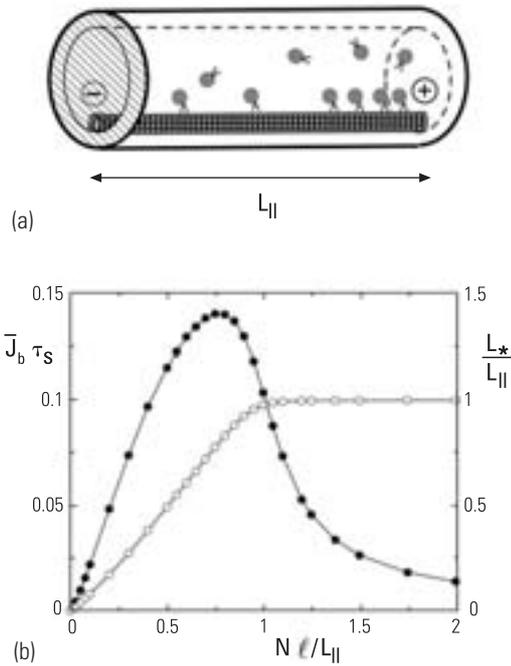


Fig. 3: (a) Closed tube with a fixed number of cargo particles. Each particle carries a certain number of molecular motors which can bind to the filament; and (b) Bound current  $J_b$  (full circles) and jam length  $L^*$  (open circles) as a function of the total number  $N$  of cargo particles. The parameters  $L_{||}$ ,  $l_{ell}$ , and  $\tau_s$  are the longitudinal extension of the tube, the step length, and the step time, respectively.

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# Theoretical Evolutionary Ecology



## Evolutionary Dynamics of Single Species

One of the most studied systems in Ecology and Evolution is the biology of plant's seeds.

Seeds offer not only for their enormous social and economical relevance scientists a number of still unresolved challenging questions.

Seeds are living embryos whose development stops until favourable environmental conditions are met for germination. During their development, the mother plant makes a series of investments in terms of energy spending to produce a different number or a different quality of seeds. The amount of seeds produced and their quality are the result of an evolutionary process driven by the interaction of the species with its environment.

Just before seeds become ripe and fall down, they start a process of dehydration, which keeps their internal structure of membranes and compartments intact and at rest. When development starts again, the membranes of the seed get hydrated and oxygen flows inside. In few hours, the entire molecular machinery is at work again. Signals trigger the development which depends on the biology of the plant but also on the predictability of the environment.

The extreme case comes from plants living in a desert, where yield can vary greatly from one season to the other and sometimes no seeds at all are produced. In such environments, only those species can survive, whose seeds germinate only with a certain probability. There we speak of "delayed germination" or "dormancy" (Fig. 1).

In the desert, vegetation is limited to few months in winter, before the temperature rises so much that all plants die. Winter can be pretty good or very bad depending on whether it rains enough or not. During bad years, the plants cannot reach maturity and produce seeds. If all seeds had germinated with the first rain, a bad year would mean the extinction of that species. That is why seeds of desert plants germinate only with a certain probability, even if conditions are optimal. This ensures that permanent seed-bank remains buried in the ground and allows spreading the risk of extinction over many seasons.

Is there any rule telling us how large should be this germination probability? Early models for seed-bank dynamics [1, 2] mapped the problem onto a random walk  $X(t+1)=R(t)+X(t)$  where  $X(t)$  is the logarithm of the size of the seed bank in season  $t+1$  and  $R(t)$  contains the contributions of the weather in season  $t$  and depends on the germination fraction  $g$ .

In natural systems, morphs of the same species carrying different  $g$  struggle for the same limited resources. Any choice of  $g$  is therefore a strategy and the search is for the optimal. This occurs through an evolutionary process driven by invasion: Any resident strategy  $g$  will be threatened by the arrival of some invader  $g'$  whose seed-bank obeys the dynamic equation  $X'(t+1)=R'(t)+X(t)$  where  $R'$  will depend also on the  $g$  of the resident. The invader will be successful and replace the resident if the time-average of  $R'$  will be positive. This process will go on until a stable strategy is established, which cannot be invaded. This is the Evolutionary Stable Strategy.

This simple model for delayed germination has been very successful because it gives a clear justification of the selective advantage of a certain germination probability.

In addition, the model implied also that the seed-bank should be uniform in  $g$ . Several empirical studies however have demonstrated that the seed-bank is not homogenous. Indeed, seeds produced after very abundant good seasons have a lower germination probability than those produced after a bad and dry season.

To find out whether these results make sense, together with Dr. Katja Tielbörger of the University of Potsdam we have developed a model to prove that such kind of behavior is better than the uniform- $g$  strategy. In fact, we needed to relax the assumptions of the early models by allowing for such variability in  $g$  to appear. We have then let the system evolve and find its Evolutionary Stable Strategy, which was always with the  $g$  after a good season smaller than the  $g$  after a dry season (Fig. 2).

This kind of behavior is interpreted as a response to the expectation of a stronger competition after an abundant season. At the level of the seeds instead, this means that the plants have more resources to invest in the membranes covering the seeds when weather conditions are optimal. This poses the question of what is the chemical and mechanical basis of delayed germination, a phenomena which is still poorly understood.

## From one Species to Ecosystems

What determines the number of species, i.e. biodiversity in an ecosystem? How are these species distributed among trophic levels? What is the effect of processes like migration on this structure? How does the number of species scale with the area of the location? These are some of the questions that many theoretical ecologists, most of them physicists, try to answer by means of mathematical models and computer simulations. These are also some of the questions that arise from field ecologists interested in general trends and concepts and from environmentalists trying to find the best solution to safeguard biodiversity.

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Ecosystems are characterized by a continuous turnover of species. There are processes like immigration, which are the source of newcomers, and there is population dynamics, with competition and predation, which is the source of extinction. In any natural system therefore, biodiversity is maintained as the result of a balance between these two competing mechanisms. Any stationary structure and distribution therefore carries the fingerprint of these mechanisms.

If we see a natural community with all links connecting the interacting species, this looks like a network [3]. This kind of ecological networks are known since long for being organized in a large-scale structure like trophic levels with remarkable stability properties. In a recent attempt to connect processes to structure, together with Tiziano Zito, now at the Humboldt University in Berlin, we have developed a computer model that extends previous work [4, 5].

In this model, only the average properties in each trophic level are computed and the fluctuations around the averages are substituted by fictitious distributions.

The existence of these distributions reflects the fact that populations in the same trophic level might have (a) quite different sizes or (b) quite different predatory efficiency. In fact, both case are present in natural systems, but the advantage of the simulation is that we could take them in account separately. In case (a), are random effects that shape the size-distribution and therefore extinction is almost independent of competition. In case (b), extinction is the result of competition alone.

Coupled to a stochastic dynamics which mimics the process of immigration, the systems show remarkable differences in the two formulations.

In case (a) indeed, the stationary distribution of species in trophic levels sees the first level as the most diverse one. In this case, moreover, the total number of species  $S$  scales like  $\sim R^{1/2}$  with the extensive resources  $R$  that might represent an area. In case (b) instead, competition introduces a scale in the system and depending on the value of the other parameters, the most populated level can be higher then the first. Here the scaling with the resources is just logarithmic, in agreement with previous results [4, 5]. Fig. 3a, b is a cartoon of a possible community for cases (a) and (b) respectively. The figures show that the number of species in each level is lower in case (b) than in (a) and that in case (b) the number of levels is typically larger than in case (a).

Further developments will go in the direction of comparing these models to empirical data and molecular-data approaches.

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Fig. 1: *Senecio Glaucus*. The seeds of this species germinate only with 10-25 % probability under optimal conditions.

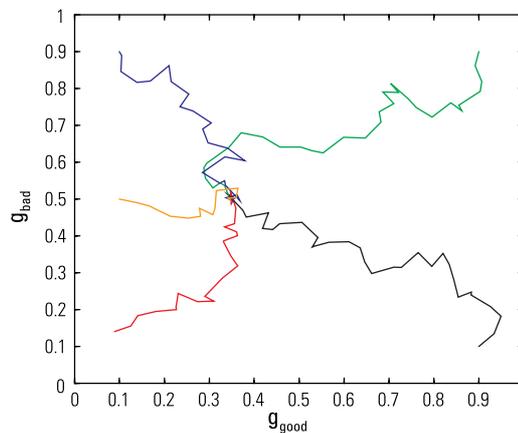


Fig. 2: All evolutionary paths lead to the same stable strategy. On the x-axis the  $g$  after a good season, on the y-axis the  $g$  after a bad season

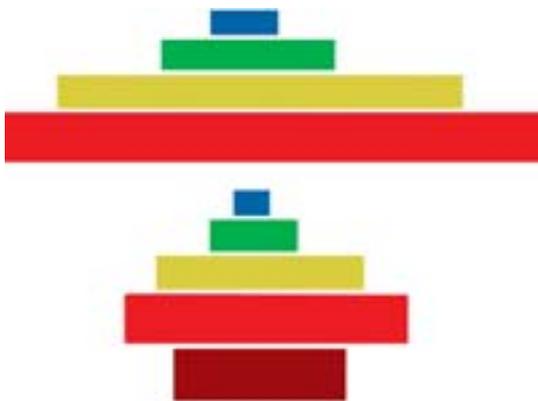


Fig. 3: a) The first trophic level is the most populated. The food-chain is short. b) The most populated trophic level is the second. The system is not very populated and the food-chain is longer.

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